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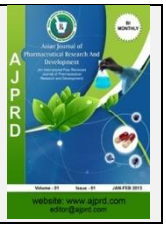

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Research Article

Formulation and Evaluation of Microspheres for Colon Targeted Drug Delivery Using Anthelminthics Drugs

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A B S T R A C T

The objective of this study was to develop sustained release microspheres for colon-targeted drug delivery system to enhance therapeutic efficacy while minimizing systemic side effects. The controlled and prolonged release of drugs in the colon can significantly improve the treatment outcomes for various colon-related diseases. Microspheres, small spherical particles with sizes ranging from 1 to 1000 micrometers, were formulated using biodegradable polymers and natural materials to ensure biocompatibility and controlled drug release. The formulation process involved the selection of appropriate polymers, such as poly lactic acid and polyglycolic acid, and the incorporation of the drug within the microspheres. Various techniques, including solvent evaporation, coacervation, and spray drying, were employed to prepare the microspheres with the desired drug-loading efficiency and particle size distribution.The formulated microspheres were extensively evaluated to assess their suitability for sustained release colon-targeted drug delivery. Evaluation parameters included drug encapsulation efficiency, particle size distribution, surface morphology and in vitro.In vitro drug release studies were conducted using simulated gastrointestinal fluids to mimic the conditions in the gastrointestinal tract. The sustained release microspheres exhibited controlled drug release over an extended period, specifically in the colon region. This sustained release profile was achieved by optimizing the polymer composition and formulation parameters, which allowed for the gradual degradation of the microspheres and subsequent release of the drug.

Keywords: Microspheres, colon targeted microspheres, sustained drug release, solvent evaporation.

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INTRODUCTION

Colon-targeted drug delivery systems (CDDS) have gained significant attention in recent years due to their potential to improve the treatment of local diseases affecting the colon while minimizing systemic side effects.[1-4]The advantages of colon-specific drug delivery include targeted treatment of colonic diseases, such as inflammatory bowel disease, irritable bowel syndrome, and colon cancer, localized treatment with reduced systemic side effects, improved bioavailability of poorly absorbed drugs, and the ability to deliver proteins and peptides that are typically administered by injections.[5-7]However, there are also disadvantages and limitations associated with colon-targeted drug delivery. Some disadvantages include elevated plasma levels of drugs due to longer residence time in the colon, unintentional disintegration of single-unit formulations, difficulties in developing colon-specific drugs due to biological barriers, lower affinity of drug-metabolizing enzymes in the colonic mucosa, and challenges with dissolution for water-soluble drugs in the low fluid volume of the colon.[8]The limitations of colon-specific drug delivery systems include the need for the drug to be in solution form before reaching the colon, low fluid content and high viscosity of colonic contents, potential non-specific binding of drugs to dietary residues and fecal matter, degradation of drugs by colonic microflora, lower surface area and tight junctions in the colon affecting drug absorption, and slow onset of action.[5,6]Factors Influencing Colon-Specific Drug Delivery: Several factors influence colon-specific drug delivery and colonic bioavailability, including anatomical/physiological factors (such as pH variation, transit time, fluid volume, and viscosity of colonic

contents), colonic enzymes and metabolism, and formulation factors (such as physicochemical properties of drugs, dose, and dosage form factors). The variability in these factors can pose challenges in the development of effective colon-targeted drug delivery systems.[9]

Microspheres:

Microspheres are tiny, spherical particles that are used as carriers for delivering drugs in a controlled and targeted manner. They are designed to release the medication gradually, providing continuous and lasting therapeutic effects. Microspheres can be made from various materials, including natural polymers like albumin and gelatin, as well as synthetic polymers like poly lactic acid and polyglycolic acid.[10]The advantages of using microspheres as drug carriers include improved solubility of poorly soluble drugs, steady drug levels in the blood, reduced toxicity and dosage, protection against enzymatic and photolytic degradation, increased bioavailability, and improved patient compliance. Microspheres can also mask taste and odor, solidify liquids for handling, protect drugs from environmental factors, enhance powder flow, and aid in the dispersion of water-insoluble compounds.[11]However, there are also some disadvantages associated with microspheres. They can be more expensive compared to conventional formulations, and the stability and environmental impact of the polymer matrix and additives used in microsphere preparation need to be considered. Reproducibility can be challenging, and the stability of the core particles can be affected by various process variables. Additionally, the degradation products of polymers may have environmental implications.[12]

Ideal microspheres should have the ability to incorporate high drug concentrations, be stable with a therapeutically acceptable shelf life, control particle size and dispersibility in injection vehicles, provide controlled release of the drug over a desired time frame, and be susceptible to chemical manipulation. They should also exhibit biocompatibility and regulated biodegradability.The preparation of microspheres involves various techniques, and factors such as particle size, route of administration, drug release duration, and specific characteristics related to the preparation process need to be considered. The criteria for microsphere preparation include the ability to incorporate high drug concentrations, stability with a suitable shelf life, controlled particle size and dispersibility, controlled release of the drug, and susceptibility to chemical manipulation, while ensuring biocompatibility and regulated biodegradability.[13-15]

MATERIALS AND METHOD

Materials:

The drug Domperidone is procured from yarrow chem products Mumbai. Mebendazole was provided as gift sample from sequent Scientific limited mahad, Maharashtra. Eudragit S100, Acetone, Liquid paraffine and span 80.

Method:

Pre-formulation Studies

Compatibility Studies- Drug Polymer Interaction (FTIR Studies) The FT-IR spectrum of Albendazole, Mebendazole and polymers was recorded using KBr mixing method on the FT-IR instrument (Schimadzu FTIR instrument). The drug alone, and in combination with polymers (mixed in the ratio of 1:1) was taken and subjected to FT-IR studies.

Preparation of Albendazole and Mebendazole Microspheres:

Microspheres were prepared by solvent evaporation method. Accurately weighted Eudragit S-100 were dissolved in 10ml of acetone to form a homogenous polymers solution. Core material, i.e. Drugs was dispersed in it and mixed thoroughly. This organic phase was slowly poured at 15°C into liquid paraffin (100 ml) containing 1% (w/w) of Span-80 with stirring at 1400 rpm to form a uniform emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-walled, rigid and discrete Microspheres were formed. The Microspheres were collected by decantation and the product was washed with petroleum ether (40– 60°C), four times and dried at room temperature for 3 hrs. The Microspheres were then stored in a desiccator over fused calcium chloride.

Table: 1 Composition of Albendazole microsphere; solvent evaporation method

Sr no.	Ingredients	X1	X2	X3	X4	X5
1	Albendazole	100 mg	200 mg	300 mg	400 mg	500 mg
3	Acetone	10ml	10ml	10ml	10ml	10ml
4	Eudragit S100	100mg	100mg	100mg	100mg	100mg
5	Liquid paraffin	100ml	100ml	100ml	100ml	100ml
6	Span 80	1% w/w	1% w/w	1% w/w	1% w/w	1% w/w

Table 2: Composition of Mebendazole microsphere; solvent evaporation method

Sr no.	Ingredients	Y1	Y2	Y3	Y4	Y5
1	mebendazole	100 mg	200 mg	300 mg	400 mg	500 mg
3	Acetone	10ml	10ml	10ml	10ml	10ml
4	Eudragit S100	100mg	100mg	100mg	100mg	100mg
5	Liquid paraffin	100ml	100ml	100ml	100ml	100ml
6	Span 80	1% w/w	1% w/w	1% w/w	1% w/w	1% w/w

Table 3: Formulation of microspheres with Drugs combination

Sr no.	Ingredients	X3(Albendazole)	Y2 (Mebendazole)
1	Drugs (mg)	300 mg	200 mg
2	Acetone	10ml	10ml
3	Eudragit S100	100mg	100mg
4	Liquid paraffin	100ml	100ml
5	Span 80	1% w/w	1% w/w

EVALUATION PARAMETER OF MICROSPHERES:

1. Percentage Yield :[16]

To prepared microsphere of all batches accurately weight. The measured weight of prepared microspheres was divided by total amount of all excipient and drug used in preparation of microspheres, which give the total percentage yield of total microspheres 15

It was calculated by following equation:

$$\% \text{ yield} = \frac{Actual \text{ weight of product}}{\text{Total weight of excipient and drug}} \times 100$$

2. Particle size:[17]

Particle size was measured by using microscopy technique. Stage micrometer was mounted in the stage. Eyepiece micrometer was fitted in the eyepiece of microscope for its calibration. Eyepiece micrometer was calibrated by coinciding with stage micrometer scale.

It was observed that, 8th division of eye piece = 10th division of stage micrometer

But, each division of stage micrometer: = 10 µ

So, 1 division of eyepiece = 100/8 = 12.5 µ

Stage micrometer was removed from the stage and sample was placed on the clean slide. Slide holding sample was mounted on the stage and observed with the help of eyepiece micrometer scale. Divisions of eyepiece micrometer scale was measured for the particle and calculations were carried out by multiplying the divisions with factor 12.5µ.

3. Swelling Index:[16]

The swelling indexes of the formulated microspheres were performed phosphate buffer pH 6.8 At 37.5+0.5°C for 8 hours. Drug loaded microspheres were equilibrated in different test tubes and at every one-hour interval; microspheres were withdrawn filtered transferred into a small beaker and weight.

The swelling ratio was calculated from the followed expression,

$$\text{Swelling index} = \frac{Wf - Wo}{Wo} \times 100$$

Where, Wf= weight of microspheres observed at every time interval

Wa =initial weight of microspheres.

4. % Drug Entrapment Efficiency:[18]

50 mg of microspheres were dispersed in 10 ml PBS pH 6.8 for 10 min with occasional shaking. The suspension was then centrifuged for 5 min and the supernatant was kept aside. The sediment microspheres were then incubated for 48 hrs with PBS pH 6.8 and the drug concentration was determined spectrophotometrically by UV at 334 nm (Shimadzu Pharmspec UV-1700, Japan). The entrapment efficiency and were calculated by using following formulas (Garud and Garud, 2011b):

$$\% \text{ Entrapment Efficiency} = \frac{Dcal}{Dth} \times 100$$

where, Dcal is the calculated drug content and

Dth is the theoretical drug content, respectively.

5. Drug Content:[19]

Drug content study the drug content of microsphere was determined by spectrophotometrically at 361 nm and 241 (Model No. 1700 PC- Shimadan, Japan). Each determination was made in triplicate. 32-35 Drug content were calculated by using following formula

Drug Content=Conc.× dilution factor volume/1000.

6. Scanning Electron Microscopy:[17]

The surface morphology of prepared microspheres was observed under scanning electron microscope (JEOL, JSM-T, Japan). Dry microspheres were placed on an electron microscope brass stub and coated with gold to a thickness of about 200 A° using a sputter coater in an ion sputter. Pictures of the microspheres were taken by randomly scanning the stub with the help of SEM analyzer

7. In-Vitro Dissolution Study:[16]

The drug release rate from the microspheres was studied in a medium of changing pH using the USP dissolution apparatus II at 37±0.5 °C with a rotation speed of 100 rpm. A weighed amount of microspheres (equivalent to 50 mg of drug) put in muslin cloth and tied to paddle, the dissolution medium consist 350 ml of 0.1N HCl, pH 1.2 for the first two hours. At the end of second hour, the pH of the dissolution medium was raised to 4.5 by the addition of 250 ml solution composed of 3.75 g of KH2PO4 and 1.2 g of NaOH. At the end of fourth hour pH was raised to 7.4 by adding 300 ml of phosphate buffer concentrate (2.18 g of KH2PO4 and 1.46 g of NaOH in distilled water) (El-Bary et al., 2012). At predetermined time intervals, 5 ml sample was withdrawn, passed through a 0.45 µm membrane filter (Millipore). After appropriate dilutions, the concentration of drug in samples was analysed spectrophotometrically at predetermined λ max(s). The initial volume of dissolution medium was maintained by adding 5 ml of fresh dissolution medium after each withdrawal. The cumulative % drug release was calculated and a graph of % cumulative vs. time was plotted.

RESULTS AND DISCUSSION

PRE-FORMULATION STUDIES

Compatibility Studies - Fourier transforms infrared spectroscopy (FTIR)

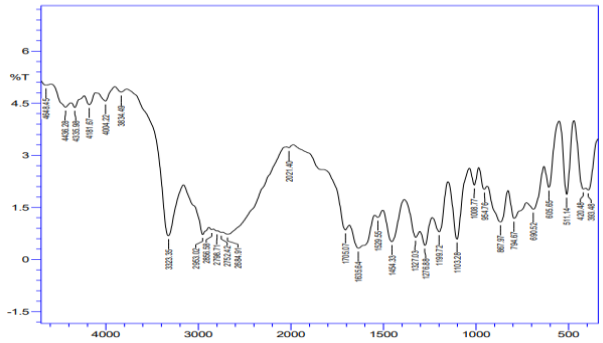


Figure 1: FTIR Spectrum of drug Albendazole

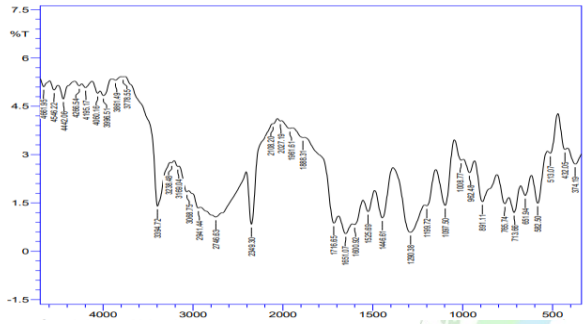


Figure 2: FTIR Spectrum of drug Mebendazole

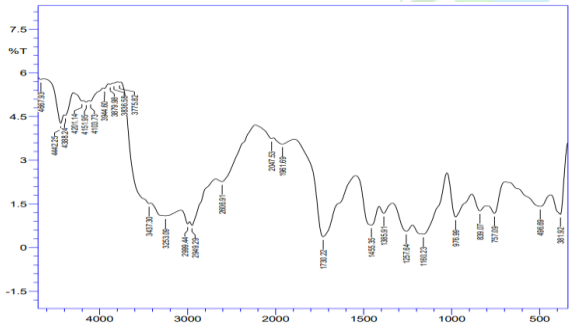


Figure 3: FTIR Spectrum of Eudragit S-100

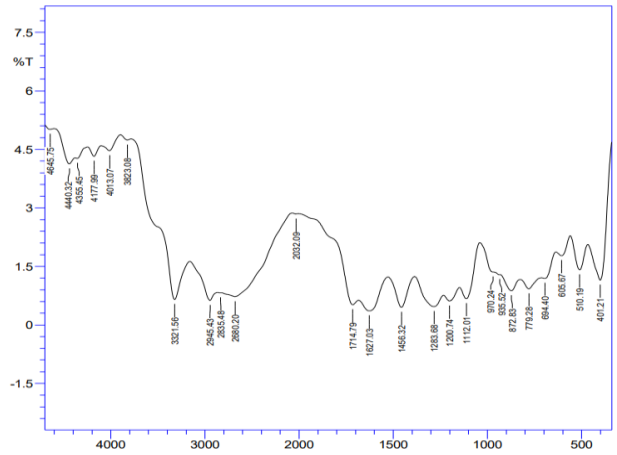


Figure 4: FTIR Spectrum of Albendazole and Eudragit S100

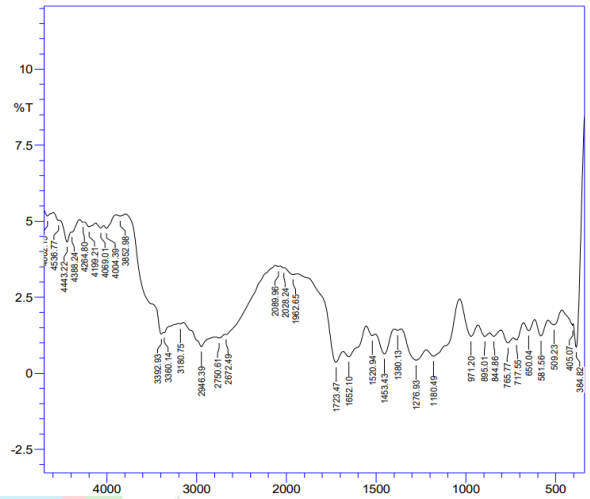


Figure 5: FTIR Spectrum of Mebendazole and Eudragit S-100

POST-FORMULATION STUDIES

1. Percentage Yield

The prepared batches of microspheres were evaluated for percentage yield. The percentage yield of microspheres was determined by calculating theoretical yield and practical yield.

Table 4: Percentage Yield (Albendazole)

Formulation batches	Percentage yield, (%)
X1	39.65±0.22
X2	78.5±0.28
X3	89.7±0.34
X4	64±0.42
X5	65.61±0.45

*Each value is mean of three consecutive reading ± standard deviation

Table 5: Percentage Yield (Mebendazole)

Formulation batches	Percentage yield, (%)
Y1	31±0.12
Y2	93.7±0.23
Y3	80.375±0.28
Y4	76.04±0.32
Y5	69.16±0.40

*Each value is mean of three consecutive reading ± standard deviation

The given data represents the percentage yield of different formulation batches, denoted as X1, X2, X3, X4, and X5. Comparing the values, we observe that batch X3 has the highest percentage yield (89.7%), followed by X2 (78.5%) and X5 (65.61%).

In the case of Mebendazole, the data shows that batch Y2 has the highest percentage yield, indicating that this formulation process is highly efficient in producing Mebendazole.

2. **Particle size**

Table 6: Particle size (Albendazole)

Formulation batches	Particle Size in (µm)	Comments
X1	118-312	Desired particle sizes were obtained
X2	125-329	Desired particle sizes were obtained
X3	162-375	Desired particle sizes were obtained
X4	180-475	Desired particle sizes were obtained
X5	212-550	Desired particle sizes were obtained

Table 7: Particle size (Mebendazole)

Formulation batches	Particle Size in (µm)	Comments
Y1	151-382	Desired particle sizes were obtained
Y2	121-318	Desired particle sizes were obtained
Y3	169-396	Desired particle sizes were obtained
Y4	198-424	Desired particle sizes were obtained
Y5	179-418	Desired particle sizes were obtained

3. **Swelling Index**

Table 8: Swelling Index (Albendazole)

Formulation batches	Swelling Index
X1	28.18±0.02
X2	32.3±0.08
X3	42.62±0.14
X4	35.73±0.18
X5	38.45±0.12

*Each value is mean of three consecutive reading ± standard deviation

Table 9: Swelling Index (Mebendazole)

Formulation batches	Swelling Index
Y1	30.52±0.06
Y2	43.69±0.12
Y3	39.71±0.2
Y4	37.35±0.10
Y5	35.34±0.13

*Each value is mean of three consecutive reading ± standard deviation

In the case of Albendazole, the data suggests that batch X3 has the highest swelling index, indicating that this formulation may exhibit faster dissolution and release of Albendazole compared to the other batches.For Mebendazole, batch Y2 has the highest swelling index, suggesting that this formulation may have better dissolution and release characteristics compared to the other batches.

4. **% Drug Entrapment Efficiency**

Table 10: % Drug Entrapment Efficiency(Albendazole)

Formulation batches	%Entrapment
X1	78.5±0.03
X2	84.1±0.07
X3	88.79±0.13
X4	81.3±0.18
X5	70.4±0.05

*Each value is mean of three consecutive reading ± standard deviation

Table 11: % Drug Entrapment Efficiency (Mebendazole)

Formulation batches	% Entrapment
Y1	81.7±0.06
Y2	89.4±0.09
Y3	84.7±0.13
Y4	79.3±0.17
Y5	69.34±0.03

*Each value is mean of three consecutive reading ± standard deviation

From above observation table % Entrapment Efficiency of microsphere were found in the range between 69.34% to 89.4% of Albendazole and Mebendazole batches X1/Y1 to X5/Y5 it was found to be X3 batch of Albendazole have higher % The Entrapment Efficiency i.e., 88.79% and Y2 batch of Mebendazole higher % Entrapment Efficiency is 89.4%.

5. **Drug content**

The drug content of microspheres was calculated.

Table 12: Drug content (Albendazole)

Formulation batches	Drug content
X1	66.14±0.18
X2	72.4±0.13
X3	78.47±0.24
X4	62.63±0.35
X5	64.7±0.53

*Each value is mean of three consecutive reading ± standard deviation

Table 13: Drug content (Mebendazole)

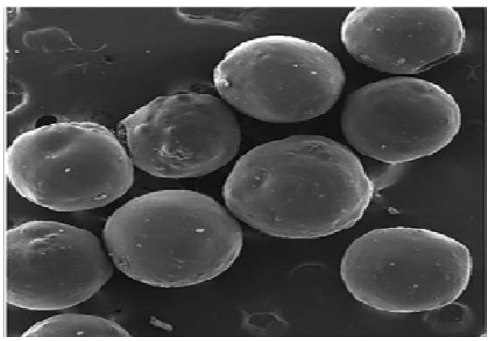
Formulation batches	Drug content
Y1	75.4±0.43
Y2	82.16±0.29
Y3	72.5±0.19
Y4	69.32±0.23
Y5	65.91±0.37

*Each value is mean of three consecutive reading ± standard deviation

From the above observation Loading efficiency of drug loaded batches was found to be 62.63% to 82.16%. The drug loading efficiency of all formulations were shown in Table No 6.15 which indicates that the highest drug content was found to be X3and Y2 as 78.47% as Albendazole and 82.16% of Mebendazole respectively. Therefore, we can conclude X3 and Y2 batch of Albendazole and Mebendazole give best result as compare to other batches.

6. **SEM studies:**

Scanning electron microscopy of the formulations revealed that the surface morphology of the prepared microspheres was found to be spherical. The surface of the spheres was rough with abrasion on it



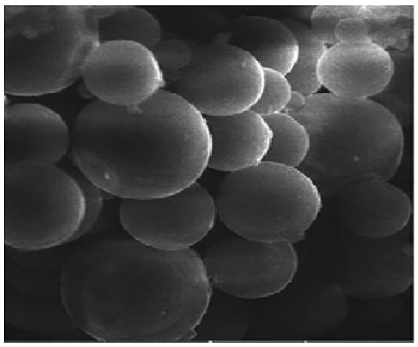


Figure 6: SEM of A) Albendazole microspheres **B)** Mebendazole microspheres

7. In-Vitro Dissolution Study

Table 14: % Drug release of Albendazole

Time (hr)	X1	X2	X3	X4	X5
0	0	0	0	0	0
1	0	0	0	0	0
2	2.575±0.95	3.328±0.43	2.855±0.56	3.934±0.86	3.616±0.56
3	5.136±0.57	7.304±0.56	6.098±0.35	8.185±0.45	6.965±0.34
4	7.699±0.56	11.192±0.45	10.34±0.65	13.165±0.56	10.324±0.63
5	10.267±0.34	14.18±0.43	13.991±0.46	18.820±0.53	13.990±0.74
6	15.838±0.45	17.264±0.45	18.642±0.93	21.99±0.56	21.438±0.63
7	19.404±0.43	22.279±0.24	21.775±0.45	26.676±0.34	28.441±0.69
8	24.978±0.56	24.62±0.46	25.953±0.45	31.827±0.63	32.826±0.34
9	27.636±0.59	29.613±0.97	30.842±0.56	35.400±0.53	37.109±0.36
10	31.224±0.45	32.750±0.75	33.489±0.54	41.367±0.34	41.060±0.64
11	34.810±0.35	37.259±0.35	36.628±0.35	44.103±0.64	46.920±0.45
12	38.376±0.64	41.731±0.35	41.688±0.35	47.953±0.84	52.002±0.41

*Each value is mean of three consecutive reading ± standard deviation

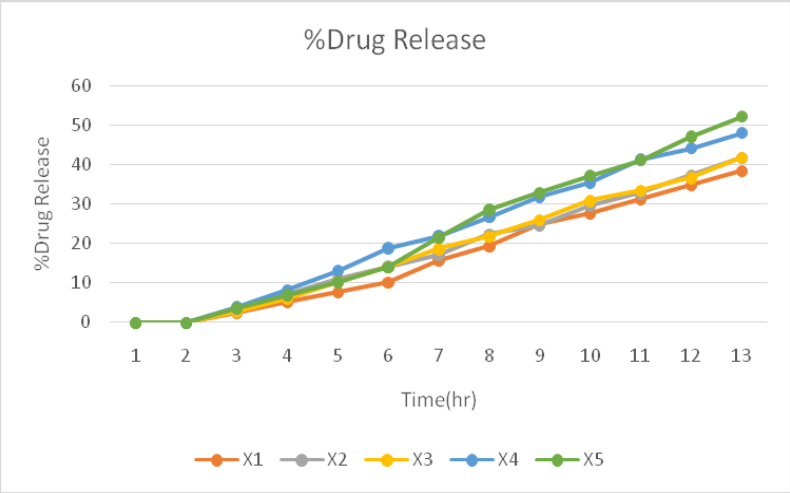


Figure 7: In vitro dissolution profile of Albendazole Microspheres.

From the above result, the drug release of formulation batches X1, X2, X3, X4 and X5 was found to 38.376%, 41.731%, 41.68%, 47.95% and 52.002% respectively. It can be observed that the formulation batch X3 batch gives most satisfactory results with sustained drug release for approximately 12hr and show highest encapsulation efficiency among the other batches.

Table 15: % Drug release of Mebendazole

Time(hr)	Y1	Y2	Y3	Y4	Y5
0	0	0	0	0	0
1	0	0	0	0	0
2	3.563±0.83	3.698±0.34	3.339±0.27	3.804±0.45	3.943±0.86
3	7.110±0.72	8.12±0.52	6.849±0.21	9.352±0.26	7.703±0.45
4	9.429±0.54	12.443±0.83	11.305±0.83	14.064±0.27	11.522±0.36
5	13.189±0.73	15.755±0.64	17.142±0.63	19.652±0.47	15.382±0.24
6	16.746±0.38	20.076±0.73	22.374±0.75	24.357±0.35	22.513±0.35
7	19.070±0.54	25.128±0.46	28.044±0.91	29.961±0.56	26.980±0.67
8	22.221±0.48	29.449±0.49	33.508±0.11	34.664±0.36	31.365±0.64
9	25.994±0.63	32.797±0.43	39.072±0.34	39.885±0.34	35.648±0.25
10	29.776±0.83	35.975±0.54	42.351±0.84	44.070±0.67	43.697±0.88
11	33.35±0.82	40.120±0.51	45.629±0.59	48.235±0.63	49.557±0.25
12	37.075±0.73	43.450±0.62	48.976±0.36	52.333±0.22	55.827±0.53

*Each value is mean of three consecutive reading ± standard deviation

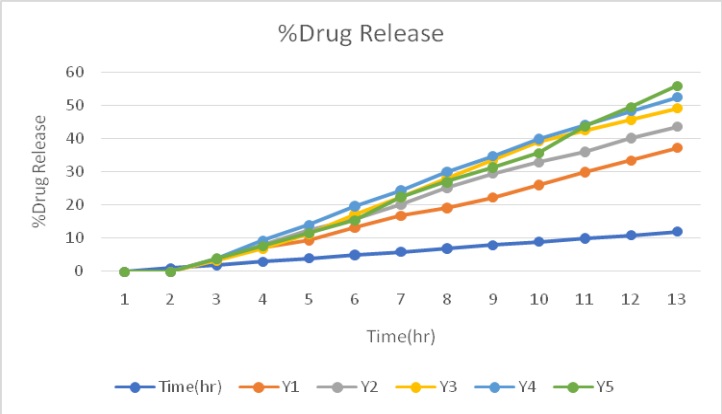


Figure 8: In vitro dissolution profile of Mebendazole Microspheres.

From the above result, the drug release of formulation batches Y1, Y2, Y3, Y4 and Y5 was found to 37.07%, 43.45%, 48.97%, 52.33% and 55.82% and respectively. It can be observed that the formulation batch Y2 batch gives most satisfactory results with sustained drug release for approximately 12hr and show highest encapsulation efficiency among the other batches.

Optimized Batch:

The combination % drug release of albendazole and mebendazole are obtained from simultaneous estimation method.

Table 16: Optimized Batch

% Drug release			
Time(hr)	**Formulation Microspheres**	**Albendazole microspheres (X3)**	**Mebendazole Microspheres (Y2)**
0	0	0	0
1	0	0	0
2	1.700±0.07	1.464±0.05	2.054±078
3	7.248±0.13	6.543±0.53	8.646±0.75
4	11.177±0.16	10.324±0.42	12.644±0.65
5	13.396±0.94	12.634±0.32	13.993±0.75
6	16.396±0.17	15.342±0.32	17.644±0.44
7	20.331±0.64	18.256±0.73	21.644±0.67
8	23.835±0.43	22.362±0.35	24.644±0.33
9	27.874±0.56	25.527±0.23	28.375±0.36
10	32.873±0.16	31.653±0.53	33.645±0.27
11	36.968±0.79	34.635±0.23	37.463±0.43
12	41.217±0.74	39.634±0.64	42.754±0.64
13	45.991±0.34	43.753±0.93	46.633±0.45
14	49.785±0.45	47.533±0.54	51.252±0.64
15	53.959±0.24	52.534±0.53	54.544±0.38
16	57.908±0.45	55.633±0.64	59.392±0.32
17	61.927±0.45	60.533±0.27	63.208±0.53
18	66.633±0.74	64.754±0.64	67.297±0.37
19	71.717±0.63	69.356±0.36	72.832±0.23
20	76.043±0.43	77.237±0.22	77.5643±0.26
21	80.824±0.74	79.367±0.34	81.076±0.74
22	85.226±0.35	84.368±0.37	86.237±0.27
23	91.552±0.34	90.261±0.36	92.246±0.53
24	97.642±0.23	96.473±0.543	98.245±0.45

*Each value is mean of three consecutive reading ± standard deviation

From the above result, the drug release of optimised batch gives most satisfactory results with sustained drug release for approximately 24 hr and show highest encapsulation efficiency among the other batches.

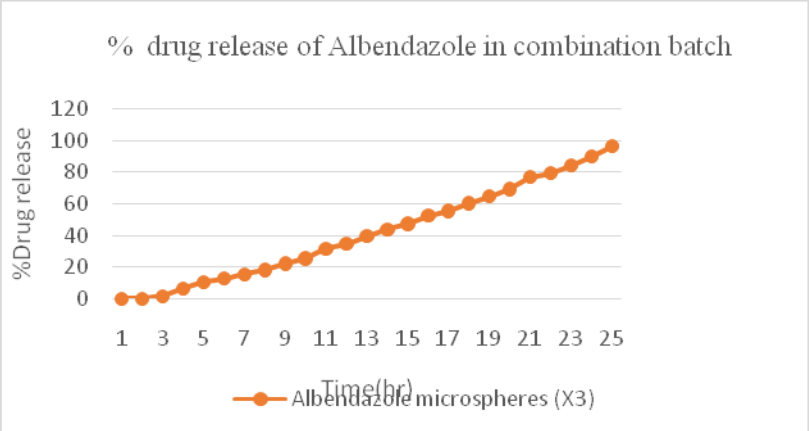


Figure 9: % Drug release of Albendazole in combination batch

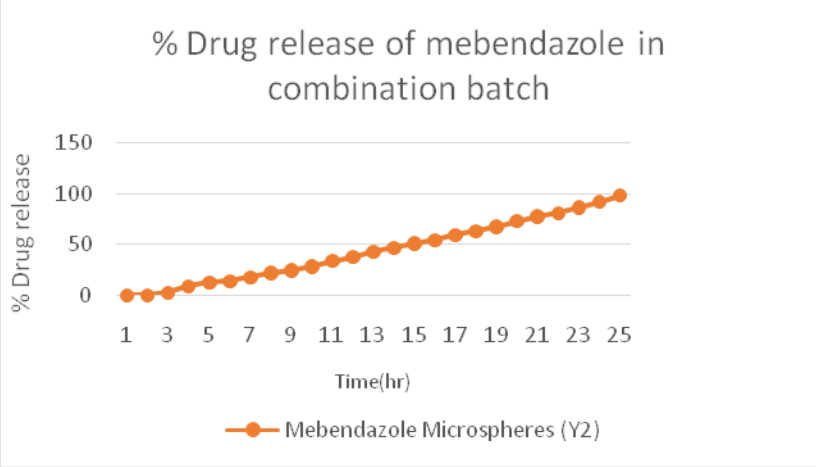


Figure10: % Drug release of Mebendazole in combination batch

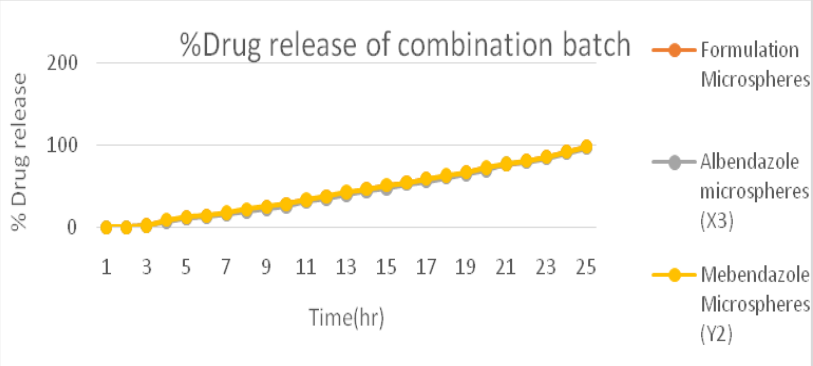


Figure 11: % Drug release in Optimized Batch

CONCLUSION

The present study has been a satisfactory attempt to formulate microspheres of Albendazole and Mebendazole with a view of improving sustain release of the drug. From the experimental results it can be concluded that, the Eudragit S-100 polymers were used which showing good sphericity and particle size. Hence, finally it was concluded that the prepared microspheres of Albendazole and mebendazole may prove to be potential candidate for safe and effective sustained drug delivery over an extended period of time which can reduce dosing frequency

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CONFLICTS OF INTEREST

The authors have no known conflict of interest concerning the present article

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